IN THE MATTER OF THE UNITED STATES PATENT APPLICATION SERIAL **NO. 09/809,173,** IN FAVOUR OF **BERNARD CHARLES SHERMAN,** APPLICANT AND THE INVENTOR OF THE SUBJECT MATTER THEREIN, FILED March 16, 2001.

DECLARATION

I, **Michael Mantle Lipp Ph.D.**, of Alkermes Inc. SOLEMNLY DECLARE AND AFFIRM THE FOLLOWING:

1. I am currently employed at Alkermes Inc. (a pharmaceutical and drug delivery technology company located in Cambridge, Massachusetts) in the position of Associate Director of Technology Development. Presently, I work in the areas of preformulation, formulation and solid-state analysis of pharmaceutical compositions for various routes of administration, including pulmonary and oral. I hold a Ph.D. in Chemical Engineering from the University of California. A copy of my curriculum vitae is attached as Exhibit A to this my Declaration. As such I believe I am well qualified to comment and provide opinion in these matters

2. The following paragraphs contain my comments and opinions concerning the United States Patent Office Examiner's rejection of claims 1 through 18 in her Final Action, dated August 19, 2003 (hereafter referred to as the Final Action), of U.S. Patent Application No. 09/809,173 entitled "Pharmaceutical Compositions Comprising Moexipril Magnesium" (hereafter referred to as the '173 patent application).

3. I was asked by Neil H. Hughes, Patent Agent of the firm Ivor M. Hughes Barristers and Solicitors, Patent and Trade Mark Agents and Counsel for the inventor Dr. Bernard Charles Sherman, to provide my opinions concerning the position taken by the United States Patent Office Examiner and her rejection of the aforementioned claims of the '173 patent application. In particular, I was asked to provide my opinions with respect to the Examiner's allegation that pending claims 1 through 18 set out in the '173

patent application are unpatentable over Gu et al. (Pharm. Res., Vol. 7, No. 4, pages 379-383) in view of Harris et al. (U.S. Patent No. 4,743,450).

4. In my opinion, the inventions described in Claims 1 through 18 set out in the '173 patent application are **not** obvious in light of the teachings and disclosures of Gu et al. in view of Harris et al. I thus disagree with the conclusions reached by the Examiner in the Final Action with respect to the '173 patent application and these references. I describe my opinions further below, beginning with a summary of the claimed inventions in question of the '173 patent application followed by my opinions with respect to the Examiner's comments and conclusions concerning the teachings and disclosures of Gu et al. and Harris et al.

Summary of the Inventions of the '173 Patent Application

5. The '173 patent application, entitled "Pharmaceutical Compositions Comprising Moexipril Magnesium" discloses processes for the production of moexipril magnesium and stable solid compositions comprising moexipril magnesium that possess advantages over alternative processing methods and formulations for the production of stabilized dosage forms containing various forms of moexipril (such as moexipril hydrochloride).

6. As described on page 1 of the '173 patent application, angiotensin converting enzyme (ACE) inhibitors such as enalapril, quinapril and moexipril, including salts thereof, are prone to degradation via the mechanisms of cyclization, hydrolysis and oxidation.

7. The inventor of the '173 patent application summarizes the art with respect to methods for improving the stability of ACE compounds such as various forms of enalapril, quinapril and moexipril in pharmaceutical dosage forms, including the references cited by the Examiner as described above (i.e., Gu et al. and Harris et al.). The majority of the references cited by the inventor of the '173 patent application, including the references cited by the Examiner, involve the addition of stabilizing agents, also

referred to as pharmaceutical stabilizers, to pharmaceutical compositions containing these ACE inhibitors. As I will describe further below, stabilizing agents are conventionally added to pharmaceutical compositions in order to inhibit and prevent the occurrence of chemical reactions such as degradation reactions in said formulations. Such stabilizers are **not** conventionally taught or known to cause or participate in reactions in said formulations or to react with drugs such as ACE inhibitors during the processing of these formulations.

8. As described in the '173 patent application, the novel processes and formulations for the production of pharmaceutical dosage forms containing moexipril magnesium disclosed in the '173 patent circumvent known problems and shortcomings inherent in alternative processes and formulations for the production of stabilized dosage forms containing moexipril hydrochloride, such as those taught and disclosed in the '450 patent. For example, it is stated on pages 3 and 4 of the '173 patent application that:

"[0014] There are certain problems inherent in the teachings of U.S. Patent No. 4,743,450. In particular:

1. The examples of U.S. Patent No. 4,743,450 indicate a ratio of magnesium carbonate to active drug from about 5.8 to about 16.5 by weight, so that it appears that the amount of magnesium compound required is large and substantially exceeds the amount of the active drug.

2. Using the approach of U.S. Patent No. 4,743,450, it is difficult to precisely control the exact final ingredients in the composition. The moexipril hydrochloride and magnesium compound are capable of an acid-base reaction. It is difficult to control the process so as to completely avoid an acid-base reaction in the making of the composition. The exact composition of the final product is thus uncertain and probably variable, if the teaching of U.S. Patent No. 4,743,450 is followed."

9. In contrast, the inventor of the '173 patent application states that the novel and advantageous features of the inventions disclosed in the '173 patent application involve processes and methods for the production of stable dosage formulations containing moexipril magnesium that (i) do not require the presence of a large excess of an alkaline stabilizer, or even the presence of any amount of an alkaline stabilizer and (ii) contain known and controlled amounts of moexipril magnesium. For example, it is stated on page 4 of the '173 patent application that:

"[0016] Improved stability is achieved by producing a dosage form which comprises moexipril magnesium.

[0017] It has been found that the magnesium salt of moexipril (i.e. moexipril magnesium) is sufficiently stable to enable stable solid compositions, without the presence of an alkaline stabilizing compound in the final composition. It has also been found that stable solid compositions comprising moexipril magnesium can be made using moexipril or an acid addition salt thereof, by reacting the moexipril or acid addition salt with an alkaline magnesium compound, so as to convert most or all (i.e. more than half) of the moexipril or acid addition salt to moexipril magnesium."

10. The '173 patent application discloses and teaches specific methods for the production of such dosage forms containing controlled amounts of moexipril magnesium (these amounts in excess of 70% of the total moexipril species present in the formulations) that do not require the presence of an excess of an alkaline stabilizer, or any alkaline stabilizer at all, to ensure formulation stability. For example, it is stated on page 6 of the '173 patent that:

"[0025] A reaction to convert the moexipril or acid addition salt thereof to moexipril magnesium cannot be accomplished simply by mixing the moexipril or acid addition salt together with the alkaline magnesium compound in dry form. It is necessary to mix and react the moexipril or acid addition salt and the alkaline

magnesium compound with the aid of solvent, and then evaporating the solvent to obtain a dry substance. The solvent will preferably be a mixture of water and organic solvent, and a preferred organic solvent is acetone. After the solvent is evaporated, the dried material obtained will be further processed into a dosage form, such as a tablet or capsule."

11. As described on pages 7 through 9 of the '173 patent application, among the specific processes and methods taught in the '173 patent application for the conversion of moexipril hydrochloride into moexipril magnesium and subsequent production of stabilized dosage forms containing moexipril magnesium are: (i) conversion in solution followed by filtering to remove excess alkaline magnesium compound, spray drying to remove the solvent and compounding with additional excipients followed by compression into tablets, (ii) conversion in solution followed by wet granulation with additional excipients for the production of tablets, (iii) wet granulation of a dry mixture of an acid addition salt of moexipril and additional excipients with a solution containing an alkaline magnesium compound for the production of tablets, (iv) wet granulation of a dry mixture of an alkaline magnesium compound and additional excipients with a solution containing moexipril or an acid addition salt thereof for the production of tablets and (v) wet granulation of a dry mixture of moexipril or an acid addition salt thereof, an alkaline magnesium compound and additional excipients with a granulating solvent for the production of tablets, with the wet granulation process itself acting to facilitate the reaction between the acid addition salt of moexipril and the alkaline magnesium compound for cases (iii) through (v). As I will describe further below, wet granulation processing methods are not conventionally taught in the art to be useful for facilitating the occurrence of reactions between formulation components to a significant extent.

12. The invention of the '173 patent application is essentially summarized and captured in Claims 1 (independent process claim) and 14 (independent formulation claim) of the '173 patent application. For example, Claim 1 states:

"Claim 1 (currently amended): A process of making a solid pharmaceutical composition comprising moexipril magnesium, said process comprising the step of reacting moexipril or an acid addition salt thereof with an alkaline magnesium compound in the presence of a sufficient amount of solvent so as to convert at least 70% of the moexipril or moexipril acid addition salt to moexipril magnesium."

Similarly, Claim 14 states that:

"Claim 14 (currently amended): A solid pharmaceutical composition comprising moexipril wherein at least 70% of the moexipril present in the composition is moexipril magnesium."

13. With respect to the remaining claims of the '173 patent application, Claims 2 through 4 and 15 through 18 essentially describe a procedure utilizing an evaporative process such as spray-drying to remove the solvent vehicle utilized to facilitate the reaction between the moexipril acid addition salt and the alkaline magnesium compound, Claims 5 through 8 describe variations of wet granulation processes utilized to effect the reaction between the moexipril acid addition salt and the alkaline magnesium compound, Claims 9 through 11 further specify Claims 1 through 3 and 5 through 8 with respect to the identity of the solvent (Claim 9), the form of moexipril (Claim 10) and the alkaline magnesium compound (Claim 11). Similarly, Claims 12 and 13 further specify Claims 1 through 3 and 5 through 8 with respect to the percentage of moexipril magnesium resulting from the disclosed processes as greater than 80% (Claim 12) or 90% (Claim 13).

The Examiner's Assertions Concerning the Obviousness of the Claims of the '173 Patent Application in Light of the Teachings and Disclosures of Gu et al. and Harris et al.

14. In the Final Action, the Examiner states that claims 1 through 18 of the '173 patent application are unpatentable over Gu et al. in view of Harris et al. With respect to the teachings and disclosures of Gu et al., the Examiner states that this reference teaches a process that results in the stabilization of moexipril hydrochloride via a reaction with an alkaline stabilizing agent (the Examiner admits that this reference does not teach the use of an alkaline magnesium compound). For example, the Examiner states on page 3 of the Final Action that:

> *"**Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexipril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate (see reference pages 379-383 and Tables).** Gu teaches that through wet granulation procedure, alkalizing agents were found to be effective in stabilizing moexipril hydrochloride in the solid state (pg. 383, col. 1). It is postulated that the stabilization results from the neutralization of the acidic drug by basic excipients at the outer surface of the granulated material. In addition, Gu teaches that it is also possible that a portion of the moexipril hydrochloride was converted to the cation salts through granulation and these cation salts degraded much slower in the solid state (pg. 383, cols 1-2)."* (Emphasis added.)

15. With respect to the teachings of Harris et al., the Examiner claims that this reference also teaches the stabilization of ACE inhibitor drugs via reaction of these drugs with alkaline stabilizers, preferably alkaline magnesium compounds. For example, it is stated on pages 3 and 4 of the Final Action that:

> *"Harris teaches a process of making a solid pharmaceutical composition comprising a method of stabilizing ACE inhibitor drugs (enalapril, quinapril, indolapril) in combination with an alkaline magnesium compound – magnesium carbonate as the stabilizer, acid addition salts (hydrochloride), a solvent (water) and various excipients (see reference column 1, lines 15-63); col. 3, line 60 through col. 4, line 68). The instability of the ACE inhibitor drugs can be*

stabilized by including an alkaline stabilizer. Salts of alkali and alkaline earth metals are operable, however magnesium, calcium and sodium are preferred, wherein magnesium is most preferred (col. 3, lines 25-39). The amount of stabilizer used will be between 1% and 90% (col. 3, lines 40-45). Examples A, B and D demonstrate tablets comprising an ACE inhibitor (quinapril) in combination with a stabilizer (magnesium carbonate) wherein a wet granulation method was used. ***Since a wet granulation procedure was used, one of ordinary skill in the art would have expected the ACE inhibitor drug and the alkaline compound to react through ionic interactions.***" (Emphasis added.)

16. The Examiner claims that the combined teachings of these two references thus makes obvious the inventions of the '173 patent application (noting that the Examiner states on page 6 of the Final Action that the Harris et al. reference was relied upon for the teaching of an alkaline magnesium compound). For example, it is stated on page 4 of the Final Action that:

"Therefore, it would have been obvious to one of ordinary skill in the pharmaceutical art at the time the invention was made to include an alkaline stabilizer, particularly an alkaline magnesium compound as instantly claimed, with an ACE inhibitor drug because the active ingredients or drugs will be preserved from cyclization and hydrolysis and in addition will have greater storage stability and be rendered more suitable for use in drug combinations. The expected result would be an improved stabilized composition for the effective treatment of hypertension."

17. I disagree with the Examiner with respect to her assertions concerning the teachings and disclosures of Gu et al. and Harris et al. As I describe further below, in my opinion, no combinations of the teachings and disclosures of these two references make obvious the inventions of the '173 patent application, including the combination of the teachings and disclosures of the Gu et al. reference in light of the teaching of an alkaline magnesium compound as a stabilizer for ACE inhibitor formulations in Harris et al. In

particular, it is my opinion that the assertions made by the Examiner in the Final Action concerning the teachings and disclosures of Gu et al and Harris et al. and their relevance to the '173 patent application are incorrect for the following reasons, among others:

(i) Gu et al. does not teach or disclose a stabilizing reaction between moexipril hydrochloride and an alkaline compound that results in significant conversion of moexipril hydrochloride into a cation salt form such as moexipril sodium.

(ii) Gu et al. teaches that the use of an alkaline compound consisting of an inorganic salt of a Group II metal (calcium carbonate), similar to an alkaline magnesium compound, does not result in adequate stability.

(iii) Harris et al. teaches the use of alkaline magnesium compounds as conventional pharmaceutical stabilizers in formulations containing ACE inhibitors, which implies that these alkaline magnesium compounds act to inhibit reactions involving ACE inhibitor drugs in said formulations.

(iv) Harris et al. thus does not teach or disclose a stabilizing reaction between moexipril hydrochloride and an alkaline compound that results in significant conversion of moexipril hydrochloride into a cation salt form such as moexipril sodium.

(v) Harris et al. does <u>not</u> teach or claim that wet granulation processes or other processes involving the presence or use of water during formulation are an essential part of the invention.

(vi) Harris et al. teaches and claims that both alkaline and saccharide stabilizers are required to be present for the production of pharmaceutical dosage forms containing ACE inhibitors possessing adequate stability.

18. Further, it is also my opinion that the Gu et al. and Harris et al. references in part both in teach away from each other and teach away from the inventions of the '173 patent application. I describe my opinions further below with respect to the teachings and disclosures of these two references and the additional comments made by the Examiner concerning these references.

Teachings and Disclosures of Gu et al.

19. The Gu et al. reference, entitled "Drug-Excipient Incompatibility Studies of the Dipeptide Angiotensin-Converting Enzyme Inhibitor, Moexipril Hydrochloride: Dry Powder vs Wet Granulation", describes the results of incompatibility studies involving the ACE inhibitor moexipril hydrochloride in combination with various pharmaceutical excipients and methods of tablet formulation.

20. The authors of this article found that most of the excipients that they examined catalyzed the degradation of moexipril hydrochloride when formulated or combined with moexipril hydrochloride in the dry state, including lactose, sodium carbonate and sodium bicarbonate, with the percent degradation increasing as a function of increasing humidity. In contrast, as shown in Table IV of this reference, Gu et al. found that mixtures of moexipril hydrochloride with various alkaline compounds in addition to lactose in the ratio 5:45:50 moexipril hydrochloride:lactose:alkaline component (wt:wt:wt) formulated via the use of a lab-scale wet granulation process showed increased stability with respect to powders of similar compositions formulated in the dry state (the stability testing conditions utilized were 60 °C and 0 or 50% RH for 13 days). As also shown in Table IV, it was observed that wet granulated mixtures containing either sodium carbonate or sodium bicarbonate as the alkaline compound displayed significantly better stability of moexipril hydrochloride than wet granulated mixtures containing calcium carbonate (98 to 99% moexipril hydrochloride remaining for the sodium forms vs. 91% remaining for calcium carbonate).

Gu et al. does not teach or disclose a stabilizing reaction between moexipril hydrochloride and an alkaline compound that results in significant conversion of moexipril hydrochloride into a cation salt form such as moexipril sodium

21. With respect to the stability results described above, in my opinion, Gu et al. does not teach or disclose a stabilizing reaction between moexipril hydrochloride and an alkaline compound that results in significant conversion of moexipril hydrochloride into a cation salt form such as moexipril sodium. In contrast, the authors of this article teach that the likely mechanism behind the increased stability results seen for these mixtures containing moexipril hydrochloride in addition to alkaline sodium compounds produced via wet granulation is due to an increase in the local micro-environmental pH at the outer surface of granules of moexipril hydrochloride due to the presence of the alkaline compound. For example, it is stated on page 383 of this reference that (column 1):

> *"Via wet granulation, alkalizing agents were found to be effective in stabilizing moexipril HCl in the solid state.* ***Supported by the product distribution profile, the stabilization is postulated to result from the neutralization of the acidic drug by basic excipients at the outer surface of the granulated material.*** *It is also possible that a portion of the moexipril HCl was converted to the cation salts via granulation and these cation salts degraded much slower in the solid state."* (Emphasis added.)

22. With respect to the product distribution profile referred to in the statement above, it is also stated on page 383 of this reference that (column 1):

> *"The product formed in the presence of basic excipients shifted from largely DKP 2 for dry powder mixtures to largely DKP 2 and hydrolysis product 3 for wet granulated materials.* ***The appearance of the latter product clearly demonstrates the neutralizing effect of the basic excipients on drug raw material in wet granulations (see Scheme I).***" (Emphasis added.)

23. Scheme I referred to in the statement above refers to moexipril solution stability data cited by the authors earlier in this reference as a motivating factor for their selection of alkaline compounds for the production of stable dosage formulations containing moexipril hydrochloride. As described on page 381 of this reference, Gu et al. found that, in solution, the degradation rate and degradation mechanism of moexipril was extremely sensitive to solution pH. For example, it is stated on page 381 of this reference that (column 2):

> *"**In solution, the DKP formation rate was extremely sensitive to pH (11-13).** For example, we have shown that moexipril hydrochloride in aqueous solution (see Scheme I) degraded mainly to DKP 2 via spontaneous k_o and k_o' cyclization processes at pH values below 4.5 (11). **At pH values between 4.5 and 10, moexipril hydrochloride degradation rate was about 10 times slower than that in acid and the major product formed was diacid 3 via a spontaneous ester hydrolysis k_o" process.** At pH values above 10, the degradation rate increased linearly with the activity of hydroxide ion (a_{OH}) due to the specific base-catalyzed k_{OH} ester hydrolysis process (see Scheme I).*
>
> ***Thus, even though it was well documented in the literature that acids and bases are generally incompatible in the solid state (1), the solution data suggested that basic excipients may provide a stabilizing effect to moexipril in the solid state by neutralizing, at the reaction site, the acidic nature of the hydrochloride salt."*** (Emphasis added)

24. Thus, Gu et al. clearly teach that the enhanced stability of moexipril hydrochloride in the presence of alkaline sodium compounds in formulations produced via wet granulation is likely due to a buffering, or neutralization, of the acidic environment at the surface of granules of acidic moexipril hydrochloride by the alkaline sodium compound. Additionally, as also evidenced by the quote from page 383 of this reference shown in paragraph 21 above, Gu et al. clearly make a distinction between

neutralization as a buffering, or pH-adjusting, effect versus a direct reaction between the acidic salt form of moexipril hydrochloride and an alkaline sodium compound.

25. Thus, I disagree with the Examiner with respect to her assertion that Gu et al. teaches a process that results in the stabilization of moexipril hydrochloride via a reaction with an alkaline stabilizing agent. For example, as described above, the Examiner states on page 3 of the Final Action that:

> *"**Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexipril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate (see reference pages 379-383 and Tables).** Gu teaches that through wet granulation procedure, alkalizing agents were found to be effective in stabilizing moexipril hydrochloride in the solid state (pg. 383, col. 1). It is postulated that the stabilization results from the neutralization of the acidic drug by basic excipients at the outer surface of the granulated material. In addition, Gu teaches that it is also possible that a portion of the moexipril hydrochloride was converted to the cation salts through granulation and these cation salts degraded much slower in the solid state (pg. 383, cols 1-2)."* (Emphasis added.)

As I described above, Gu et al. clearly teach towards the role of the alkaline component as being a buffering or neutralizing agent that acts to inhibit the degradation of moexipril hydrochloride in the formulations produced by wet granulation described in this reference. As I will describe further below with respect to the teachings of Harris et al., this is in agreement with the conventional definition of a pharmaceutical stabilizer as being a compound which acts to inhibit the occurrence of reactions involving drugs in pharmaceutical formulations, not to facilitate or to participate in them.

26. Additionally, as evidenced by many standard tablet formulation textbooks and references, the state of the art concerning tablet formulation teaches that the common tablet formulation process known as wet granulation is typically utilized to improve the

compressibility and flowability of tablet powder mixtures in order to improve their processability. These references typically do not teach or describe the use of wet granulation processes to facilitate reactions between formulation components. For example, Chapter 3 (entitled "Compressed Tablets") from the well-known textbook entitled "Pharmaceutical Dosage Forms - Tablets" (Lieberman and Lachman, Editors, included here as Exhibit B to my Declaration) contains an extensive description of the wet granulation process and its advantages and disadvantages. With respect to the standard definition of a wet granulation process, it is stated on page 116 of this reference that:

> *"Wet granulation consists of moistening the mixture of active ingredient and diluent with the granulating liquid comprising the binder in solution in water, alcohol, or mixture of these two, or any other acceptable liquid* ***to moisten and bind the powders together by causing the particles to adhere to each other.*** *"* *(Emphasis added.)*

27. Thus, this standard reference teaches that the purpose of a granulating liquid is to cause granules or particles of drugs and excipients to adhere to each other, not to dissolve and to react with each other (i.e., the binding liquid is described to coat and bind the particles, not to dissolve them). Similarly, when discussing the advantages of wet granulation, it is stated on pages 114 and 115 of this reference that:

> ***"The purpose of granulation is to enlarge the particle size of a powder and obtain uniform particles which will flow readily through the tablet machine hopper and feed frames into the dies.*** *This results in a number of improvements in the properties of the powder with regards to tableting.*
>
> *1.* ***The cohesiveness and compressibility of powders is improved due to added binder which coats the individual powder particles, causing them to adhere to each other so they can be formed into agglomerates, called granules.*** *Thus, by this method, the properties of formulation components are modified to overcome their tableting deficiencies. During the compaction process, granules*

are fractured, exposing fresh, clean powder surfaces, and this also improves compressibility. Lower pressures are therefore needed to compress tablets-resulting in improvements in tooling life and machine wear.

2. High-dosage drugs having poor flow or compressibility properties must be prepared by wet granulation to obtain suitable flow and cohesion for compression. In this case, the proportion of binder required to impart adequate compressibility and flow is much less than the proportion of dry binder needed to produce a tablet by direct compression.

3. Good distribution and uniform content for soluble low dosage drugs and color additives is obtained if these are in the binder solution of a wet granulation. This represents a distinct advantage over direct compression, where content uniformity of drugs and uniform color dispersion can be a problem.

4. Wet granulation prevents segregation of components of a homogeneous powder mix during processing, transferring, and handling. In effect, the composition of each granule becomes fixed and remains the same as-or very nearly that of-the powder mixture at the time of liquid-binder addition.

5. The dissolution rate of a hydrophobic drug may be improved by wet granulation with the proper choice of solvent and binder."

28. In my opinion, such information would **not** teach a skilled formulator that a wet granulation process can allow for a significant amount of reaction to occur between granular formulation components initially present in a dry state as part of a powder mix before the liquid of granulation is added, as is the process described in the Gu et al. reference. The combining of solid granules of drugs and excipients in a wet granulation process is very different than a reaction occurring between solubilized drug and excipient components in an equilibrium solution. A wet granulation process presents both kinetic and solubility limitations with respect to the ability of formulation components to dissolve and react to an appreciable extent during wet granulation processing, due to (i) the limited amount of water present and (ii) the fact that the wetted granulation is typically only mixed over short time periods (minutes) before the granulation is dried. It would not be evident to a skilled formulator that enough time and solvating power would

exist in such a process to allow for such a reaction to occur between formulation components to an appreciable extent.

29. This information concerning conventional wet granulation processes is also supported by the mechanism of stabilization postulated to occur by Gu et al. as described above, namely, the neutralization of the acidity of the drug at the interface between the granular formulation components and the liquid of granulation (water). This implies that the granules of moexipril hydrochloride do not dissolve to an appreciable extent in the granulating liquid.

30. Finally, as noted by the Examiner as described above with respect to the teachings of Gu et al., one reference is made in this article concerning the possibility for the observed enhanced stability of moexipril hydrochloride to be due in part to the conversion of moexipril hydrochloride into a cation salt. In particular, it is stated on page 383 of Gu et al. that (column 1):

> *"Via wet granulation, alkalizing agents were found to be effective in stabilizing moexipril HCl in the solid state. Supported by the product distribution profile, the stabilization is postulated to result from the neutralization of the acidic drug by basic excipients at the outer surface of the granulated material.* ***It is also possible that a portion of the moexipril HCl was converted to the cation salts via granulation and these cation salts degraded much slower in the solid state.*** *"* (Emphasis added.)

31. The statement shown above is the only reference made in this entire article to a potential reaction occurring between moexipril hydrochloride and an alkaline or basic component. Gu et al. only refer to the possibility of a portion of the moexipril hydrochloride converting to the cation salt; it is not taught that such a reaction, if it occurs at all, occurs to an appreciable extent. Additionally, assuming that such a reaction even does occur, there are no teachings provided in Gu et al. concerning either (i) to what extent such a reaction does occur and (ii) if this reaction occurs in a controlled manner to

result in the formation of a significant and reproducible amount of a cation moexipril salt in the wet granulation formulations disclosed in this reference. It is thus not my opinion that this single statement would teach a skilled formulator that a controlled reaction occurs between moexipril hydrochloride and an alkaline compound in the wet granulation formulations described in the Gu et al. reference that results in significant conversion of moexipril hydrochloride into a cation salt form.

32. Thus, for the reasons described above, I disagree with the Examiner with respect to her assertion that Gu et al. teaches a process wherein moexipril hydrochloride is stabilized via a reaction with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate. In addition, I disagree with the Examiner with respect to her comments concerning a lack of distinction between a reaction occurring between formulation components versus the mixing of formulation components. In particular, the Examiner states on page 6 of the Final Action that:

> *"The applicant's argument that a combination of ingredients rather than a reaction is taught is not persuasive. The term "reacting" is generic. One definition of "reacting" is the interchange of constituents with other substances. The mixing of the ingredients (as taught by Gu and Harris) constitutes this interchange."*

I disagree with the Examiner with respect to this point. With respect to the matter at hand, in my opinion, there is a clear distinction between a chemical reaction in which two compounds react chemically to produce two or more different compounds versus the physical mixing of formulation ingredients.

Gu et al. teaches that the use of an alkaline compound consisting of an inorganic salt of a Group II metal (calcium carbonate), similar to an alkaline magnesium compound, does not result in adequate stability

33. As I described above in paragraph 20, Gu et al. teaches that wet granulated mixtures containing either sodium carbonate or sodium bicarbonate as the alkaline compound display significantly better stability of moexipril hydrochloride than wet granulated mixtures containing calcium carbonate (as shown in Table IV from Gu et al., 98 to 99% moexipril hydrochloride remaining for the formulations containing alkaline sodium compounds vs. 91% remaining for formulations containing calcium carbonate). Calcium carbonate is an inorganic salt of a Group II metal (calcium), which is also the case for magnesium carbonate. This would indicate to a skilled formulator that different results could be obtained for formulations containing ACE inhibitor drugs in combination with Group I alkaline salts (i.e., sodium salts) versus Group II alkaline salts (i.e., calcium or magnesium salts). As I will describe further below, Harris et al. teaches the preferred use of alkaline magnesium (Group II) salts as stabilizers in pharmaceutical formulations containing ACE inhibitors. Thus, in my opinion, Gu et al. and Harris et al. thus teach away from each other with respect to the use of Group II alkaline salts, including alkaline magnesium salts, in stabilized pharmaceutical formulations containing ACE inhibitor drugs.

Teachings of Harris et al.

34. Harris et al. (U.S. patent 4,743,450, hereafter referred to as the '450 patent) discloses and claims formulations and processes for the creation of stable dosage forms containing certain ACE inhibitors. In particular, Harris et al. discloses that the formulations and processes taught and claimed in the '450 patent serve to minimize the occurrence of drug degradation via cyclization, hydrolysis and coloration in various dosage forms containing these ACE inhibitors. Whereas the text of the '450 patent and the formulation examples contained therein refer to quinapril hydrochloride as the ACE inhibitor, the inventors list structurally related drugs such as enalapril and indolapril as also being particularly valuable for use in practicing the inventions of the '450 patent (see column 2, lines 32 through 34 of the '450 patent).

Harris et al. teaches the use of alkaline magnesium compounds as conventional pharmaceutical stabilizers in formulations containing ACE inhibitors, which implies that these alkaline magnesium compounds act to inhibit reactions involving ACE inhibitor drugs in said formulations

35. The inventors of the '450 patent teach that stability of the ACE inhibitors is provided for by the inclusion of pharmaceutical stabilizers in the disclosed dosage formulations that include both alkaline stabilizers, such as alkaline magnesium compounds, as well as saccharide stabilizers, such as lactose. For example, it is stated in column 3 of the '450 patent that (lines 25 through 29):

> *"The cyclization and hydrolytic instability which are exhibited by certain of the drugs discussed above can be overcome via the use of a suitable quantity, i.e., an effective amount of an* ***alkaline stabilizer****, together with saccharides."* (Emphasis added.)

Similarly, it is stated in column 1 of the '450 patent that (lines 56 through 63):

> *"III. A method of making a pharmaceutical dosage form which comprises the step of including in the formulation suitable amounts of:*
>
> *(a) an ACE inhibitor, and*
>
> ***(b) stabilizers which contain alkaline agents alone or alkaline agents in combination with saccharides (i.e., sugars) as one or more cyclization, hydrolysis, and discoloration inhibitor(s).***" (Emphasis added.)

36. Thus, Harris et al. teach the use of alkaline and saccharide **stabilizers** in pharmaceutical formulations containing ACE inhibitor drugs. Pharmaceutical stabilizers are known in the art to be compounds that are added to pharmaceutical formulations for the purpose of inhibiting or preventing reactions involving drugs contained in said formulations from occurring. For example, a stabilizer is defined in the reference entitled

"Hawley's Condensed Chemical Dictionary" (included here as Exhibit C to my Declaration) as (page 1042):

> *"**stabilizer**. Any substance that tends to keep a compound, mixture, or solution from changing its form or chemical nature. Stabilizers may retard a reaction rate, preserve a chemical equilibrium, act as antioxidants, keep pigments and other components in emulsion form, or prevent the particles in a colloidal suspension from precipitating. See inhibitor."*

Such stabilizers are typically added to pharmaceutical formulations to maintain their stability during the period after which they have been produced (i.e., over the shelf-life of the final formulation). Thus, such a stabilizer would need to be present in the final formulation in its original (i.e. unreacted) form in order to perform its function over the shelf-life of the formulation.

37. Thus, as would be understood by persons skilled in the area of pharmaceutical chemistry, stabilizers used in standard pharmaceutical practice are molecules that inhibit or prevent reactions between active ingredients and other chemical species in pharmaceutical formulations. An example of such stabilizers are antioxidants that are commonly included in pharmaceutical formulations to prevent oxidative reactions from occurring that can transform or degrade active ingredients contained in these formulations. An additional example particularly relevant to the matter at hand is the UNVASC® moexipril hydrochloride formulation cited by counsel for the inventor of the '173 patent application in the Response to Official Action of March 21, 2002, Amendments and Remarks dated September 18, 2002. The product monograph for the UNVASC moexipril hydrochloride formulation lists moexipril hydrochloride as being present in the final formulation in addition to magnesium oxide as an alkaline stabilizer, as per the teachings of the '450 patent which is listed on the FDA Orange Book for this formulation. As a result, in my opinion, a skilled formulator reading Harris et al. would

not expect a reaction to occur between an alkaline or saccharide stabilizer and an ACE inhibitor drug in the formulations disclosed therein.

Harris et al. thus does not teach or disclose a stabilizing reaction between moexipril hydrochloride and an alkaline compound that results in significant conversion of moexipril hydrochloride into a cation salt form such as moexipril sodium

38. In addition to defining the alkaline and saccharide compounds described in the '450 patent as stabilizers, nowhere in the '450 patent do the inventors refer to any reactions occurring between the ACE inhibitors and the alkaline stabilizers, including the alkaline magnesium compounds. Thus, I disagree with the assertions made by the Examiner with respect to this point. As I described in Paragraph 15 above, the Examiner states on pages 3 and 4 of the Final Action that:

> *"Harris teaches a process of making a solid pharmaceutical composition comprising a method of stabilizing ACE inhibitor drugs (enalapril, quinapril, indolapril) in combination with an alkaline magnesium compound – magnesium carbonate as the stabilizer, acid addition salts (hydrochloride), a solvent (water) and various excipients (see reference column 1, lines 15-63); col. 3, line 60 through col. 4, line 68). The instability of the ACE inhibitor drugs can be stabilized by including an alkaline stabilizer. Salts of alkali and alkaline earth metals are operable, however magnesium, calcium and sodium are preferred, wherein magnesium is most preferred (col. 3, lines 25-39). The amount of stabilizer used will be between 1% and 90% (col. 3, lines 40-45). Examples A, B and D demonstrate tablets comprising an ACE inhibitor (quinapril) in combination with a stabilizer (magnesium carbonate) wherein a wet granulation method was used.* ***Since a wet granulation procedure was used, one of ordinary skill in the art would have expected the ACE inhibitor drug and the alkaline compound to react through ionic interactions.*** *"* (Emphasis added.)

39. Thus, the Examiner asserts that the use of a wet granulation process in Examples A through D from the '450 patent would indicate to a skilled formulator that the ACE inhibitor drug and alkaline compound would react. However, as I described above with respect to Gu et al, a skilled formulator would not expect that the use of a wet granulation process would result in any significant conversion of quinapril hydrochloride into a cation salt form (quinapril magnesium) in Examples A through D from the '450 patent, especially in light of the fact that magnesium carbonate is defined as a pharmaceutical stabilizer as described above.

Harris et al. does <u>not</u> teach or claim that wet granulation processes or other processes involving the presence or use of water during formulation are an essential part of the invention

40. Additionally with respect to the Examiner's assertions described above concerning the teachings of the '450 patent, the inventors of the '450 patent do not teach that a wet granulation manufacturing process is required for practicing the inventions disclosed therein, nor do they even refer to water as being required to be present during formulation processing. For example, with respect to manufacturing methods suitable for use in practicing the inventions of the '450 patent, the inventors state that (column 4, lines 26-33):

> *"Any techniques for processing the products of the invention which are appropriate can be employed. A wet granulation process is preferred."*

Thus, the inventors of the '450 patent only state that a wet granulation process is preferred, not that it, or any alternative process involving the presence of water, is required. As a result, a skilled formulator would assume that dry methods of tablet production such as direct compression or dry granulation could also be utilized.

41. Further, with respect to the types of dosage forms suitable for practicing the inventions disclosed in the '450 patent, the inventors state that (column 4, lines 36-43):

"The final form of the pharmaceutical preparations made in accordance with the invention can vary greatly. Thus, tablets, capsules, sachets, sprinklers, pomades, transdermal compositions, buccal preparations, candy compositions, nasal formulations, ocular compositions and the like are contemplated. Orally administerable forms, i.e., tablets, caplets, and capsules, are preferred."

Thus, the inventors of the '450 patent also teach that a wide range of pharmaceutical dosage forms in addition to tablets can be employed when practicing the inventions disclosed therein. Since wet granulation is a manufacturing process used primarily for tablet production, these statements indicate that a range of alternative formulation methods to wet granulation can be used to practice the inventions of the '450 patent. A skilled formulator would not expect that all, if even any, of these methods would provide for or facilitate the occurrence of a reaction between any of the formulation components. In contrast, the '173 patent application teaches the use of processes in which a sufficient amount of water is always present in order to permit the conversion of at least 70% of the moexipril hydrochloride to moexipril magnesium.

Harris et al. teaches and claims that both alkaline and saccharide stabilizers are required to be present for the production of pharmaceutical dosage forms containing ACE inhibitors possessing adequate stability

42. Additionally, the '450 patent clearly teaches that both an alkaline stabilizer and a saccharide stabilizer are required to be present ensure formulation stability. For example, it is stated in column 3 of the '450 patent that (lines 25 through 29):

"The cyclization and hydrolytic instability which are exhibited by certain of the drugs discussed above can be overcome ***via the use of a suitable quantity, i.e., an effective amount of an alkaline stabilizer, together with saccharides.***" (Emphasis added.)

43. The importance of saccharides such as lactose as key stabilizing components of the inventions of the '450 patent is clearly made evident in the patent examples. Examples A and B from the '450 patent refer to tablets made via wet granulation containing quinapril hydrochloride in combination with magnesium carbonate and lactose as stabilizers in addition to other excipients. Example C refers to tablets made with quinapril hydrochloride in combination with anhydrous lactose and acidic compounds, in addition to other excipients and water; an alkaline stabilizer is thus absent from the tablets produced in Example C. Example D refers to tablets made via wet granulation with quinapril HCl, magnesium carbonate, gelatin and magnesium stearate; these tablets did not contain a lactose stabilizer. Example E refers to the results of stability tests conducted at 60 °C for 1 month utilizing the tablets described in Examples A through D. For the tablets described in Examples A and B that contain both alkaline and lactose stabilizers, there were 97.1% (Example A tablets) and 98.1% (Example B tablets) quinapril hydrochloride remaining in the tablets after 1 month. However, for the tablets described in Example D that contained only an alkaline stabilizer (magnesium carbonate, with lactose being absent from the tablets), the quinapril hydrochloride content was reduced to 93% after 1 month, with the major degradation product being the hydrolysis product.

44. Thus, such results would teach a skilled formulator that (i) as disclosed by the inventors of the '450 patent, both alkaline and saccharide (lactose) stabilizers are required to ensure ACE inhibitor drug stability and (ii) the lactose stabilizer acts to inhibit the hydrolysis of the ACE inhibitor drugs described in the '450 patent. Thus, these results together with the specification of saccharides such as lactose as stabilizers indicate that lactose is a key stabilizing component of the invention of the '450 patent.

45. Finally, with respect to the 17 claims of the '450 patent, all 17 of these claims include the addition of both alkaline and saccharide stabilizers. For example, Claim 1 of the '450 patent describes a pharmaceutical composition containing both alkaline and saccharide stabilizers, with the saccharide stabilizer present to inhibit hydrolysis. In particular, Claim 1 states that:

"1. A pharmaceutical composition which contains:

(a) a drug component which comprises a suitable amount of an ACE inhibitor which is susceptible to cyclization, hydrolysis and discoloration,

(b) a suitable amount of an alkali or alkaline earth metal carbonate to inhibit cyclization and discoloration, and

(c) a suitable amount of a saccharide to inhibit hydrolysis." (Emphasis added.)

Similarly, Claims 2 through 15 are dependent on Claim 1 and thus also claim pharmaceutical compositions containing both alkaline and saccharide stabilizers. Similarly, Claim 16 of the '450 patent states that:

"16. A process for stabilizing an ACE inhibitor drug against cyclization which comprises the step of contacting the drug with:

(a) a suitable amount of an alkali or alkaline earth-metal carbonate and,

(b) ***one or more saccharides.*** *"* (Emphasis added.)

Claim 17 is dependent on Claim 16. Thus, all 17 claims of the '450 patent specify the inclusion of both alkaline and saccharide stabilizers in the claimed formulations and processes.

Combined Teachings of Gu et al. and Harris et al.

46. Thus, in my opinion, neither of the references Gu et al. and Harris et al. make obvious the inventions of the '173 patent application. As I described above, neither of these references teaches or makes obvious a process for the conversion of moexipril hydrochloride to moexipril magnesium via a reaction with an alkaline magnesium compound for the purpose of increased stability. Additionally, it is also my opinion that these two references in part both teach away from each other and teach away from the inventions of the '173 patent application. I thus disagree with the assertion made by the

Examiner with respect to the combined teachings of these references. For example, the Examiner states on page 6 of the Final Action that:

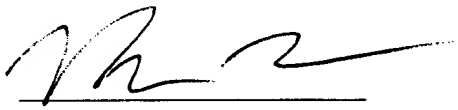
"Gu teaches a process wherein moexipril hydrochloride is stabilized by reacting the moexipril hydrochloride with an alkaline stabilizing agent, such as sodium bicarbonate, sodium carbonate, and calcium carbonate. Gu does not teach the use of an alkaline magnesium compound in the process. The secondary reference of Harris was relied upon for the teaching of an alkaline magnesium compound. Harris explicitly teaches a process of making a solid pharmaceutical composition, which comprises a method of stabilizing ACE inhibitor drugs (enalapril, quinapril, indolapril) in combination with an alkaline magnesium compound – magnesium carbonate as the stabilizer, acid addition salts (hydrochloride), a solvent (water) and various excipients. The instability of the ACE inhibitor drugs can be stabilized by including an alkaline stabilizer."

47. However, in addition to the reasons that I described above with respect to the these references considered individually, it is my also opinion that the Examiner is incorrect in asserting that these references can be read together in the manner the Examiner describes above (i.e., utilizing Harris et al. to teach the use of an alkaline magnesium compound in the processes described in Gu et al.). For example, as I described in Paragraph 33 above, Gu et al. teaches away from the use of Group II alkaline salt compounds such as alkaline calcium or alkaline magnesium compounds. In contrast, Harris et al. teaches the preferred use of an alkaline magnesium compound. Additionally, Gu et al. teaches that the use of a wet granulation process is required to obtain suitable formulation stability. In contrast, Harris et al teaches that a variety of formulation methods and pharmaceutical dosage forms can be utilized in practicing the inventions disclosed therein.

48. In summary, it is my opinion that the inventions disclosed in the '173 patent application are not made obvious by any combination of the teachings and disclosures of Gu et al. and Harris et al. Both Gu et al and Harris et al. disclose processes for the

stabilization of various ACE inhibitors and their acid addition salts, including moexipril hydrochloride, via the production of formulations containing these ACE inhibitors in their original forms (i.e., in the form of moexipril hydrochloride for Gu et al. and quinapril hydrochloride in Harris et al.) in combination with one or more pharmaceutical stabilizers such as alkaline compounds. In contrast, the '173 patent application discloses novel formulations and processes for the stabilization of moexipril hydrochloride via its conversion into the form of moexipril magnesium.

49. I solemnly declare and affirm further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereof.

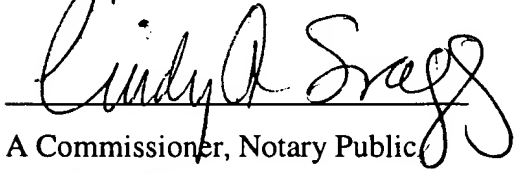


Michael Mantle Lipp

Associate Director, Technology Development

Alkermes Inc.

AFFIRMED before me)
at Middlesex County)
in Cambridge MA, U.S.A.)
this 9th day of February, 2004)



A Commissioner, Notary Public
for taking Oaths

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009

This is Exhibit A to the Declaration of Dr. Michael Lipp
Sworn on 2/9/04

Cindy A. Sragg

A Notary Public...for taking Affidavits, etc.

CINDY A. SRAGG
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My Commission Expires
January 23, 2009

Curriculum Vitae of Michael Mantle Lipp

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Education:

University of California, Santa Barbara, California
Ph.D. Chemical Engineering, October, 1997
Research Advisor: Professor Joseph A. Zasadzinski
Thesis Topic: " Microscopy of model lung surfactant monolayers"

Cornell University, Ithaca, New York
B.S. Chemical Engineering, May 1992
Graduated with distinction
Engineering Cooperative Program Participant, 1990

Experience:

Associate Director of Technology Development, 2004 - present
Pulmonary Development Division – Alkermes Inc. (www.alkermes.com)
Supervisor: Dr. Rick Batycky (Vice President, Pulmonary Development)
Positions/Focus Areas:

* **New Technology and Product Development**
  > Lead and direct group identifying and developing new technologies and product opportunities for Alkermes Inc.
  > Coordinate and direct internal research efforts and external collaborations with industrial and academic institutions
  > Direct investigation of novel particle production methods and particle applications
  > Direct development of improved dry powder inhaler systems
  > Conduct and coordinate of feasibility studies for partnered and proprietary drug formulation candidates
* **Intellectual Property Technical Leader – Pulmonary Development Division**
  > Interface with Alkermes Inc. Intellectual Property Department and Project Teams with respect to Alkermes intellectual property issues
  > Provide scientific and technical evaluations of patents and competing technologies for the Alkermes Inc. Intellectual Property Department
* **Solid State Analysis Team Leadership**
  > Coordination and conduction of solid-state analyses of AIR pulmonary formulations and Alkermes injectable formulations
  > Provide information for formulation optimization and determination of developmental history for AIR project teams (physical and chemical stability studies, comparability studies, etc.)
  > Skills/methods utilized – DSC, TGA, HPLC, SEM, vapor sorption analysis, surface area analysis, particle sizing and density determination, etc.

Staff Scientist, 2001 - 2003
Pulmonary Formulations Division – Alkermes Inc.
Supervisor: Dr. Jeff Hrkach (Director, Pulmonary Formulations)
Positions/Focus Areas:

* **Formulation and Feasibility Team Leadership**
  > Formulation – selection and testing of excipients and excipient combinations for current and new AIR product formulations
  > Production – coordination of research scale spray-drying for the production and optimization of AIR powder formulations
  > Investigation of novel particle production methods and particle applications
  > Conduction and coordination of feasibility studies for partnered and proprietary new AIR drug formulation candidates
* **Solid State Analysis Team Leadership**
  > Coordination and conduction of solid-state analyses of AIR pulmonary formulations and Alkermes injectable formulations
  > Provide information for formulation optimization and determination of developmental history for AIR project teams
* **CMC Team Leadership**
  > Experience with CMC team leadership (two small molecule project teams)
  > Experience with IND submissions, cGMP practices, specification setting, stability study protocol determination, etc.
* **AIR Intellectual Property Technical Coordinator**
  > Technical contact for Alkermes Inc. Intellectual Property Department and AIR Project Teams with respect to intellectual property issues

Senior Scientist II, 2000 – 2001
Aerosol Science and Engineering Division - Advanced Inhalation Research
Positions:

* AIR Biomaterials Team Leader
  Responsibilities:
  > Team Leadership - manage and direct multidisciplinary team (team includes members of Engineering, Pharmaceutical Sciences, Life Sciences Divisions, etc.)
  > Preformulation and formulation of candidate AIR powder formulations
  > Solid State Characterization - manage and conduct AIR in-house and out-sourced solid state particle characterization efforts
  > New Applications - investigation of novel particle production methods and particle applications
* Powder Science and Technology Team Leader (Engineering Division sub-team)
  Responsibilities:
  > Team Leadership - manage efforts of Engineering Division Research Associate team members
  > Coordinate and conduct preformulation work for new drug formulations
  > Develop in vitro methods for monitoring particle stability and drug release
  > Develop and optimize spray-drying methods for particle production
* Aerosol Science and Engineering Group Member
  Responsibilities:
  > Feasibility and development powder production, optimization and characterization
  > Liason with Manufacturing, Pharmaceutical Sciences and Life Sciences teams.

* AIR Research Projects Team Leader
    > Management and direction of AIR research projects
    > Supervisor - Dr. David Edwards (President/CSO - AIR)
* AIR Intellectual Property Representative/Coordinator

Senior Scientist, 1998 - 2000
Aerosol Science and Engineering Division - Advanced Inhalation Research
Positions/Focus Areas:
* Powder Science and Technology Team Leader (Engineering Division sub-team)
* Team Member - Controlled Release
* Team Member: New Technology Evaluation
* Aerosol Science and Engineering Group Member

Research Affiliate, 1998 - present
Department of Chemical Engineering
Massachusetts Institute of Technology
Positions/Focus Areas:
* Research Area: Study of lipid-based drug delivery systems
* Consultant: Assist Dr. Robert S. Langer in his role as an expert consultant/witness for various companies with respect to patent-related issues

Advisor: Professor Robert Langer

Post-Doctoral Research Fellow, February 1998-September 1998
Department of Chemical Engineering
Massachusetts Institute of Technology
Research Area: Study of large porous lipid-based particles for pulmonary drug delivery
Advisors: Professors Robert Langer (MIT) and David Edwards (Penn. State University)

Post-Doctoral Research Fellow, October 1997-January 1998
Department of Chemical Engineering
University of California, Santa Barbara, California
Research Area: Study of synthetic lung surfactant via Fluorescence, Brewster Angle, and Atomic Force Microscopy
Advisor: Professor Joseph A. Zasadzinski

Research Assistant, Ph.D. Program 1992-1997
Department of Chemical Engineering
University of California, Santa Barbara, California
Research Area: Study of synthetic lung surfactant via Fluorescence, Brewster Angle, and Atomic Force Microscopy
Advisor: Professor Joseph A. Zasadzinski

Undergraduate Research Assistant, 1991-1992
Chemical Engineering Department
Cornell University, Ithaca, New York
Research Area: Surface science of semiconductor crystal growth
Advisor: Professor James R. Engstrom

Engineering Cooperative Program, Fall, 1990
Department of Energy Science and Engineering Research Semester
Oak Ridge National Laboratory, Oak Ridge, Tennessee
Research Area: Design of an energy system for a proposed lunar base, sponsored by NASA
Advisor: Dr. Mitchell Olszewski

Awards:

National Institutes of Health NRSA Individual Postdoctoral Fellowship, 1998-2000

Lancaster Award - Top thesis in Mathematical and Physical Sciences and Engineering, University of California, Santa Barbara, 1998

Corning Foundation Materials Research Graduate Student Fellowship, 1996-1997

Materials Research Society Graduate Student Award Winner, 1996

Microscopy Society of America Presidential Student Award Winner, 1996

University of California Regents Special Fellowship, 1992-1996

Publications:

1. Phase and Morphology Changes in Lipid Monolayers Induced by SP-B Protein and its Amino-Terminal Peptide
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13. Production and Characterization of Large Porous Particles for Pulmonary Drug Delivery
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2. *Modulation of Release from Dry Powder Formulations*, S. Basu, J. Hrkach, G. Caponetti, M. Lipp, K. Elbert, W. Li, U.S. Application No. 20010036481, (November 1, 2001).

3. *Lipid-Protein-Sugar Particles for Drug Delivery*, D. Kohane, M. Lipp, R. Langer, U.S. Application No. 20020150621 (October 17, 2002).

4. *Particles for Inhalation Having Sustained Release Properties*, S. Basu, J. Hrkach, M. Lipp, K. Elbert, D. Edwards, U.S. Application No. 20030118513, (June 26, 2003).

5. *Particulate Compositions for Pulmonary Delivery,* R. Batycky, D. Edwards, M. Lipp, U.S. Application No. 20030129139 (July 10, 2003).

6. *Particulate Compositions for Improving Solubility of Poorly Soluble Agents,* R. Batycky, G. Grandolfi, S. Plunkett, M. Lipp, J. Wright, U.S. Application No. 20030129250 (July 10, 2003).

This is Exhibit B to the Declaration of Dr. Michael Lipp
Sworn on 2/9/04

Cindy A Sragg

A Notary Public...for taking Affidavits, etc.

CINDY A. SRAGG
Notary Public
My Commission Expires
January 23, 2009